REMARKS

Applicants respectfully request reconsideration of this application in view of the foregoing amendment and the following remarks.

A. Status of the Claims

Upon entry of the foregoing amendments, claims 1-3, 6-8, 12-17, and 53 will remain pending in the application. Claim 3 is presently being amended solely to correct its dependency.

B. The Claims Comply with the Enablement Requirement

Claims 6-8 and 53 are rejected under 35 U.S.C. § 112 for allegedly failing to comply with the enablement requirement. According to the Examiner, modifying the charge on either the organic complex or the antigen is an uncertain process because it can induce conformational changes that impact immunogenicity. Applicants respectfully traverse the rejection.

The Office has applied an incorrect standard for enablement. As the Federal Circuit has repeatedly stated, the "test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent, coupled with information known in the art, without undue experimentation."[1] The standard is not "*a priori* predictability," which is the criterion that the Office has invoked here.

Applicants do not dispute that some modifications of charge on organic complexes and antigens can negatively impact immunogenicity; yet, it is "not a function of the claims to specifically exclude possible inoperative substances."[2] The question is not whether all embodiments are operative, but rather whether the skilled person can ascertain suitable (operative) embodiments through ordinary or routine experimentation. With respect to the subject matter of claims 6-8 and 53, it is a routine matter to determine whether any particular modification undercuts immunogenicity. Indeed, the documents cited to support the enablement rejection evidence just how ordinary such empirical experimentation was, even years ago. Additionally, there is an extensive, pre-filing literature concerning the modification of protein charge, via 6K and 6H polybasic tails, for performing chelation chromatography. For instance, see U.S. patents No. 5,284,933 (Dobeli *et al.*) and No. 4,569,794

[1] *U.S. v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989).

[2] *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569 (Fed. Cir. 1984).

(Smith *et al.*), attached here as Appendices I and II, respectively. Proteins modified to permit use of such purification processes are known to consistently to yield conformationally correct proteins.

Thus, claims 6-8 and 53 are enabled because methodology for modifying the charge on organic complexes and antigens were well known, at the time of filing, and because it was a routine matter to determine whether particular modifications affect immunogenicity. The Federal Circuit has made it clear that "routine experimentation does not constitute undue experimentation."[3]

Additionally, Applicants wish to emphasize that conformational correctness is not an essential requirement of the claimed invention. Cytotoxic T cell and CD4+ T helper cell responses do not require conformationally correct antigens. Accordingly, there is no reason to expect that the addition of a polybasic tail, for example, to antigens would affect their usefulness.

Because the Office applied an incorrect standard for enablement, and because practicing the claimed invention would require no more than routine experimentation, Applicants respectfully request withdrawal of the enablement rejection.

C. The Claims are Patentable over WO 98/22135

Claims 1, 3, an 12-17 stand rejected under 35 U.S.C. § 102(a) as allegedly anticipated by WO 98/22135 ("Berglindh"). According to the Office, "the lipid aggregate of Berglindh specifically combines saponins with phosphatidyl inositol, phosphatidyl glycerol, phosphatidic acid and/or lipid A." Although the Office agrees that Berlindh does not suggest any particular arrangement of saponin and a sterol, it asserts that the rejected claims likewise do not recite a particular arrangement between the saponin and sterol.

Applicants respectfully traverse the rejection. The rationale for this rejection rests on a factual error, concerning the work of memorialized in the reference.

Berglindh did not combine saponin with sterol, as the rejected claims require. Rather, Berglindh relates to a combination of saponin with phospholipids, such as phosphatidyl inositol, phosphatidyl glycerol, phosphatidic acid and/or lipid A. Phospholipids are not sterols, and the two are not equivalent for purposes of the claimed invention.

As explained in Applicants' response dated December 17, 2004, which is incorporated by

[3] *Johns Hopkins University v. Cellpro, Inc.*, 152 F.3d 1342 (Fed. Cir. 1998).

reference, Berglindh does not suggest a "complex" of saponin and sterol, as presently recited. Indeed, the skilled artisan would have expected that any attempt to incorporate negatively-charged saponin into Berglindh's protocol for making a cochleate/aggregate would disrupt a Ca^{2+}/lipid interaction essential to forming the cochleate/aggregate. Thus, from Berglindh's passing mention of saponin the skilled artisan would have understood that the latter could only be added to a pre-formed cochleate/aggregate structure. In this scenario, however, the saponin would not be "complexed" predictably with any other component.

To substantiate this point, Applicants have performed experiments, described in the attached declaration of John Cox, confirming (1) that saponin does not form complexes with preformed cochleates made according to Berglindh and (2) that the use of cholesterol in Berglindh's protocol results in malformed, unstable structures, which would disorganize over time and resist adequate characterization. The declaration strongly supports Applicants' previous arguments against anticipation by Berglindh.

For at least the foregoing reasons, Berglindh neither teaches nor suggests an "organic complex" comprised of saponin and sterol as "two or more different interacting chemical components" (page 9, lines 14-15). Because the claims require such a complex, the anticipation rejection is improper, and Applicants respectfully request its withdrawal.

D. The Claims are Patentable over WO 96/33739

Claims 1, 3, 12-17 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by WO 96/33739 ("Garcon"). In particular, the Office asserted that Garcon disclosed "a vaccine composition comprising an antigen combined with a saponin/sterol complex that induces a CTL response." Applicants respectfully traverse the rejection.

Garcon does not teach or suggest an immunogenic complex comprised of an organic complex and an antigen in electrostatic association. To the contrary, Garcon principally relates to liposomes that encapsulate an antigen. See, *e.g.*, page 2, lines 1 & 29-30; page 5, lines 1-4; and page 12, lines 5-6. While Garcon suggests that soluble antigens also may be "outside" the liposome, it does not even hint that such antigens are electrostatically associated with the liposome.

The disclosure of such an electrostatic association also is not inherent in Garcon. For a claimed invention to be anticipated by inherency, each element of the invention must "necessarily

[be] present in the thing described in the reference."[4] The liposomes of Garcon may or may not be electrically charged and this could vary, for example, according to the ratio of neutral and charged lipids that constitute the liposome. Likewise, the antigens of Garcon may or may not be electrically charged - Garcon lacks any teachings in that regard. It is not enough that Garcon's compositions possibly could contain a negatively charged organic complex and a positively charged antigen, that the antigen possibly could be outside the liposome and that an electrostatic association possibly could develop between the antigen and liposome. "Inherency [ ] may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."[5] Thus, Garcon does not anticipate the rejected claims.

Garcon lacks any suggestion to pair a negatively charged organic complex with a positively charged antigen, and there is no motivation to make such a pairing otherwise evidenced in the art of record. Simply put, skilled artisans did not appreciate the advantages of such a pairing, prior to the claimed invention.

Because Garcon neither teaches nor suggests pairing a negatively charged organic complex with a positively charged antigen, Applicants respectfully request withdrawal of the anticipation and obviousness rejections.

E. Double Patenting

Claims 1, 3, 6-8, 12-17 and 53 were provisionally rejected on grounds of obviousness-type double patenting over claims of copending U.S. patent application No. 10/622,470. Because the rejection is only provisional at this time, Applicants defer any argument or "corrective" action concerning the rejection until the Office allows claims in one of the copending applications.

F. Concluding Remarks

Applicants believe that this application is in condition for allowance, and therefore request favorable reconsideration of the application.

If the Examiner believes that an interview would further advance prosecution, she is invited to contact the undersigned attorney by telephone.

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[4] *Finnigan Corp. v. United States ITC*, 180 F.3d 1354, 1365, (Fed. Cir. 1999).

The Commissioner is hereby authorized to charge any additional fees that may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extensions under 37 C.F.R. §1.136 and authorize payment of any extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 26 September 2005

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[5] *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981).

Appendix I – U.S. Patent No. 5,284,933 (Dobeli *et al.*)

Appendix II – U.S. Patent No. 4,569,794 (Smith *et al.*)